CLINICAL VIGNETTE

Gastrointestinal Stromal Tumor in a Patient with Neurofibromatosis Type 1

Grace I. Chen, MD and Susan D. Leonard, MD

Case

A 65-year-old female with recurrent major depression, hypertension, neurofibromatosis type 1 (NF1) established primary care with a geriatrician shortly after becoming Medicare-eligible. She has had depression for most of her life complicated by panic attacks. Mood symptoms are often exacerbated by social stressors and she tends to treat her symptoms with a bottle of wine each night. She was also found to have osteoporosis, diabetes and hyperlipidemia. Over the next four years, she had intermittent worsening of mood, fatigue, weakness, nausea, GERD and hypertension. Exacerbations of her mood disorder and fatigue symptoms improved with decrease in alcohol intake, increase in regular physical activity and regular fluid hydration. Her gastrointestinal symptoms improved with lowering her metformin dose, increasing fluid hydration and treating constipation.

At the age of 69, she again began having "bad anxiety attacks out of the blue." These episodes persisted for the next five months. Panic attacks manifested with palpitations, shakiness and dizziness. Labs obtained showed a persistent decline in her renal function. Renal ultrasound to evaluate for acute kidney injury showed a right suprarenal mass. Subsequent magnetic resonance imaging (MRI) of her abdomen showed an adrenal neoplasm and cluster of mesenteric masses concerning for metastatic disease in the left upper quadrant. Further evaluation of the suprarenal mass revealed a pheochromocytoma. PET CT showed intense activity in the adrenal gland area without other areas of concern noted. She underwent resection of the pheochromocytoma with resolution of her panic attacks and improvement of her hypertension and hot flashes. However, she continued to have a poor appetite and constipation. Endocrine evaluation was negative for adrenal insufficiency.

Four months after resection of her pheochromocytoma, she underwent an endoscopic ultrasound of her left upper quadrant. Biopsies were not obtained to avoid spreading possible tumor. Two months later, she underwent resection of the mesenteric masses. Pathology showed three gastrointestinal stromal tumors (GISTs) in the jejunum of the small bowel measuring 3.2 cm, 0.5cm and 0.7cm in size. Pathology showed all three tumors were spindle cell type and negative for KIT and PDGFRA mutations.

Over the next two years, she continued to have intermittent nausea and abdominal pain with no evidence of recurrence of either the pheochromocytoma or GIST on abdominal imaging.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. They are believed to originate from the interstitial cell of Cajal, the gut pacemaker of the autonomic nervous gut system or related stem cells.[1,2] Pathogenesis is related to mutational activation of KIT (protoncogene for the tyrosine receptor kinase) and Platelet Derived Growth Factor Receptor Alpha (PDGFRA) genes. Primary GISTS are tumors involving these mutations and are of either the sporadic and familial type. In sporadic GISTs, these mutations only occur in the neoplastic tissue. In familial GISTs, these constitutional mutations are in every cell of the body.

Neurofibromatosis is an autosomal dominant disease first described by Von Recklinghausen in 1849. It affects approximately 1:3000 people worldwide and presents with multiple soft tissue neurofibromas, café-au-lait macules, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, central nervous system gliomas, peripheral nerve sheath tumor, macrocephaly and cognitive deficits.[3] Neurofibromatosis Type 1 (NF1) results from mutation of the NF1 gene, a tumor suppressor found on chromosome 17q11.2 that leads to its inactivation.[4] This gene mutation predisposes those who have it to neoplasms that affect the tissues of the eye, skin and nervous system.

Given their origin from cells of the autonomic nervous system of the gut, GISTs are the most common gastrointestinal NF1-associated tumors.[3] GISTs are at least 500 times more frequent in patients with NF1 compared to the general population. Interestingly, NF-1 associated GISTs have different presentations and phenotypes than primary GISTs. Whereas primary GISTs often present with gastrointestinal bleeding and can cause gastrointestinal obstruction, anemia, early satiety and abdominal distention, NF1 associated GISTs are often clinically indolent.[1-3,5-7] More NF1 associated GISTs tend to be found incidentally. Unlike primary GISTs which are primarily located in the stomach and do not occur in multiples, the ones associated with NF1 tend to localize to the jejunum/small intestines, present in multiples, lack GIST-specific mutations (KIT and PDRGFRA) and have lower mitotic rates.

Current literature demonstrates difficulty in providing prognosis in patients with GIST.[1,7] There is very little data regarding prognosis and median survival. Factors for prognostication include mitotic index, tumor size, tumor location (gastric vs non-gastric) and tumor rupture. These four factors provide more

useful information for stratification than genotype. The National Institute of Health uses risk-stratification by tumor size and mitotic index. The Miettinen and Lasota risk model incorporates tumor size, number of mitoses and tumor location.[1] Surgery is the mainstay of treatment with importance given to avoid tumor rupture. Imatinib is used to treat GISTs with detectable KIT or PDGFRA gene mutations due to its ability to inhibit the receptor tyrosine kinase driven signals.[8,9] There is no consensus on follow-up surveillance with recommendations ranging from every three to four months to annually for at least the first five to ten years.

This case describes a unique constellation of symptoms in a patient with NF1 and other co-morbidities who was later found to have GISTs. It is unclear if her gastrointestinal symptoms are related to her GISTs as the symptoms are relatively non-specific and have persisted despite resection of her lesions. There are likely contributors from her other medical conditions, including depression, diabetes, GERD, constipation and pheochromocytoma. Her GISTs are consistent with what is typically seen in NF1 associated GISTs. The lesions occurred in multiples in the jejunum and pathology showed them to be spindle type and negative for both KIT and PDGRFA mutations. Given the overlap of symptoms and also that these tumors can be clinically indolent, she will continue surveillance imaging to evaluate for recurrence.

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